CREUTZFELDT-JAKOB DISEASE SURVEILLANCE IN THE UNITED KINGDOM

Introduction

Following the advent of Bovine Spongiform Encephalopathy (BSE), both the Southwood Committee and the Tyrrell Committee recommended reinstitution of surveillance of Creutzfeldt-Jakob Disease (CJD). This project was funded by the Department of Health and commenced in May 1990. The project is in two parts: the first the clinical surveillance of Creutzfeldt-Jakob disease including a case-control study (Grant Holder Dr R.G. Will) and the neuropathological component of the study (Grant Holders Dr R.G. Will and Dr J.E. Bell). This report summarises the progress to date in relation to both the clinical and pathological aspects of the study.

SECTION 1. CLINICAL SURVEILLANCE OF CREUTZFELDT-JAKOB DISEASE

Detailed information on the epidemiological parameters of CJD is available from previous studies by Professor W.B. Matthews which cover the years 1970 to December 1984. The first task was to extend descriptive epidemiological information on CJD to cover the years 1985 to April 1990 and this has now been completed. The second task was to carry out prospective surveillance of CJD in the United Kingdom from May 1990 onwards and this is continuing. The prospective study also involves a case-control study which examines specific putatitive risk factors for CJD with particular reference to occupational incidence.

The methodology of the CJD Surveillance Programme was discussed in detail in April 1990 by the Allen Committee, a subcommittee of the expert group set up by the MRC to supervise research in the human spongiform encephalopathies. The original methodology proposed in the grant application was approved.

1. Retrospective Study of CJD: 1985 - April 1990

Cases were ascertained from death certificates provided by the OPCS and equivalent bodies in Scotland and Northern Ireland together with direct referral from neurologists, neuropathologists and electrophysiologists. A total of 260 suspect cases of CJD were ascertained and the source of these cases is documented in Table 1.

TABLE 1

1985 - APRIL 1990 SURVEY

TOTAL SUSPECT = 260

Source of Cases	No.	%
Neurologist	9	3
Pathologist	23	9
Physician	4	2
Death Certificate	216	83
Psychiatrist	1	0.4
EEG Department	4	2
Other	3	1
	260	

Hospital records were sought on all suspect cases and these were then classified according to the diagnostic criteria based on those of Masters et al. and discussed at the Allen Committee Meeting (Appendix 1). A total of 76 definite and 62 probable cases were identified for further analysis. Of the remainder, 48 were classified as possible cases and 48 as other cases. One case of Gerstmann-Straussler syndrome was identified and 25 cases were unclassifiable because further details could not be obtained.

TABLE 2

1985 - APRIL 1990 SURVEY

Classification of Cases		(n = 260) %	(n = 235) % of classifiable
Definite	76	29	32
Probable	62	24	26
Possible	48	18	20
Other	48	18	20
Unclassified	25	10	-
GSS	1	0.4	0.4
	260		

Of the 138 definite and probable cases, 80% were diagnosed by neurologists and 7% by pathologists and general physicians respectively.

The number of cases per annum is listed in Table 3 and the overall incidence over the duration of the study was 0.46/million/annum, which is entirely consistent with the previous surveys of CJD in the UK.

TABLE 3

1985 - APRIL 1990 SURVEY
(n = 138)

Year of Death	No.
1985	28
1986	26
1987	22
1988	22
1989	28
1990 (to 30 April 1990)	12

The age-specific incidence rates are shown in Table 4 and are also consistent with previous surveys. The only difference is the small number of cases in the 20-24 year age group which represent individuals who developed CJD following human growth hormone treatment.

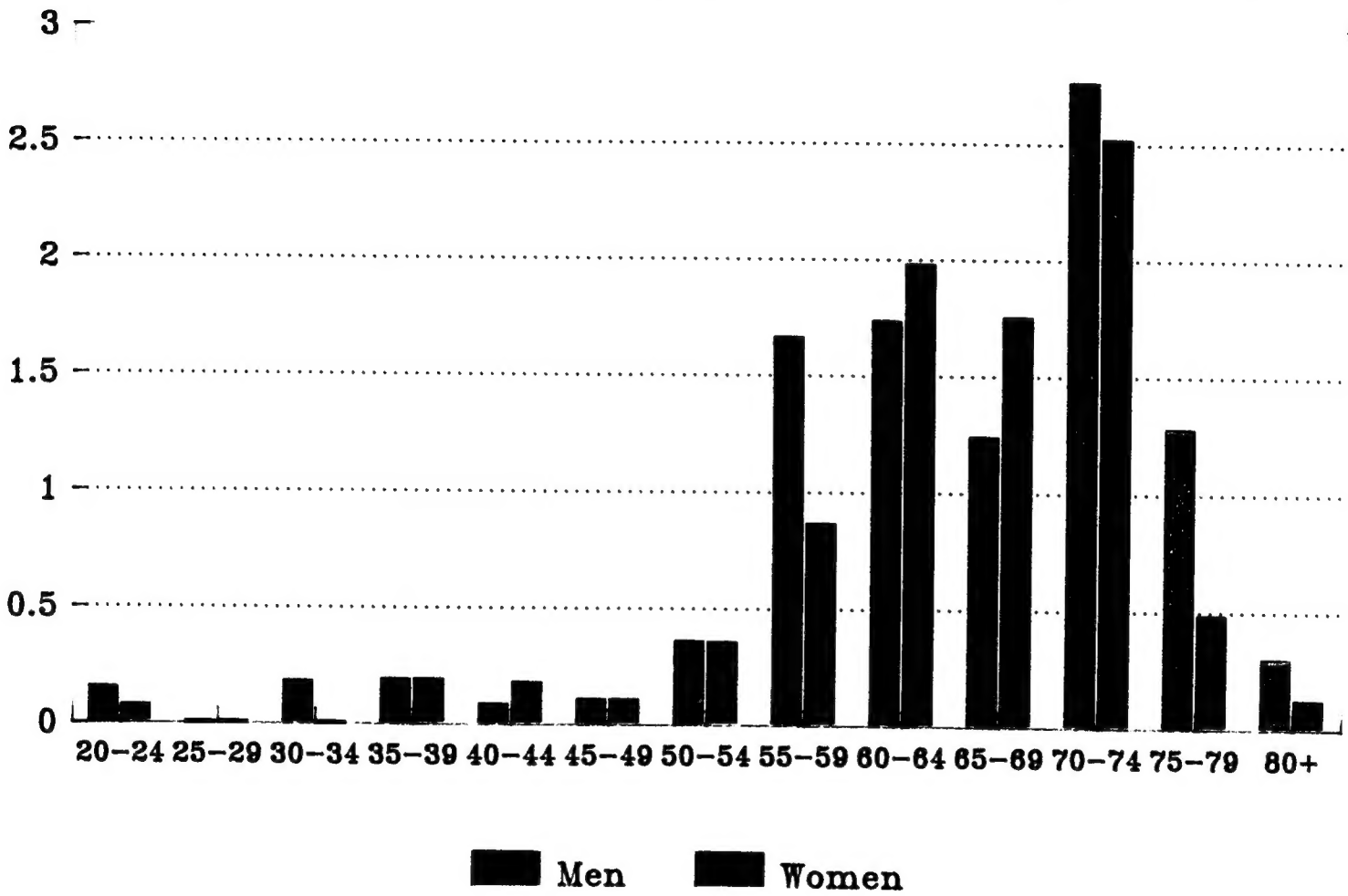
Clinical Features:

The duration of illness as defined as period from first symptom to death is shown in Table 5 and is also consistent with previous experience.

TABLE 4

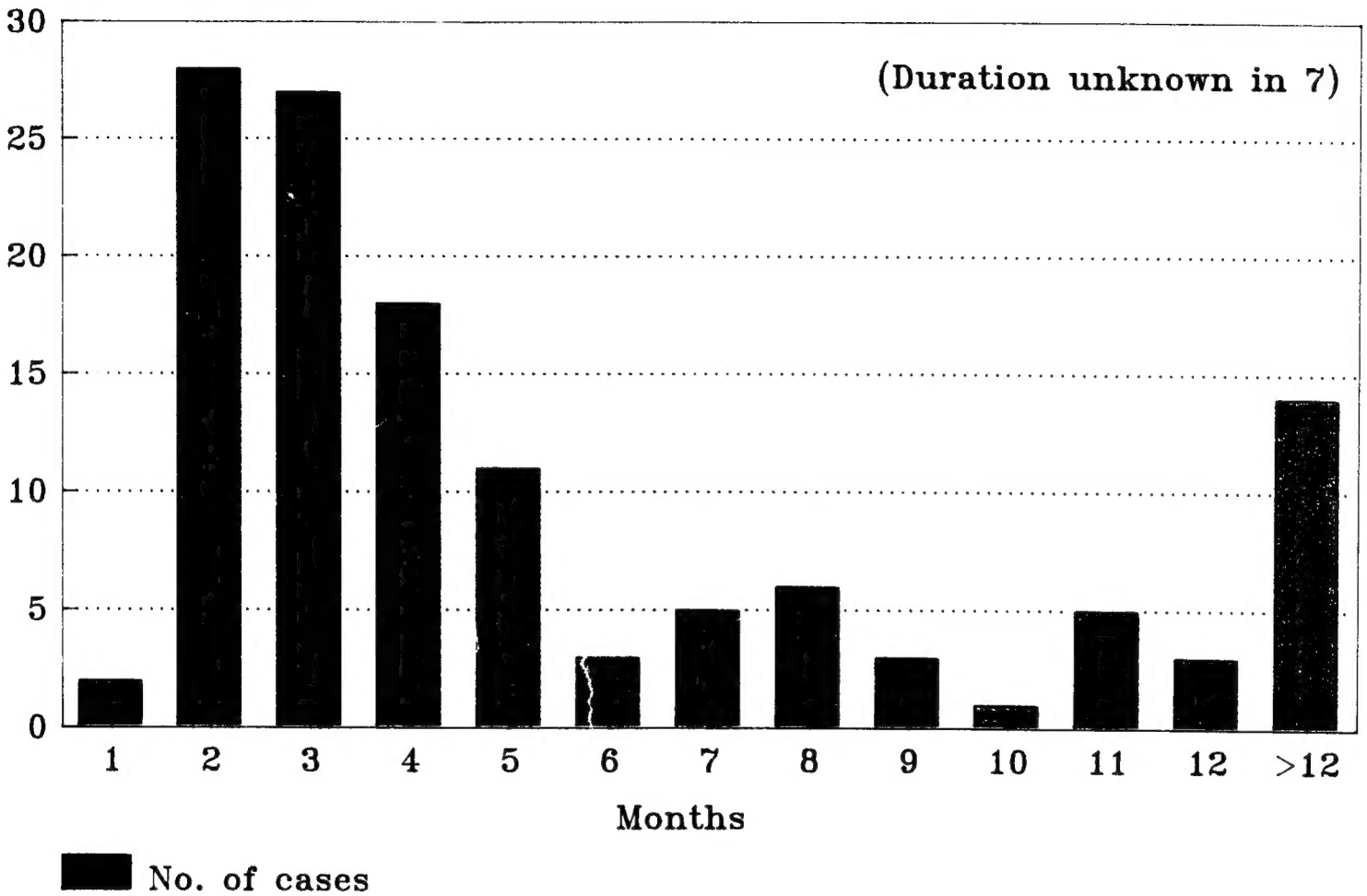
UNITED KINGDOM 1985 – APRIL 1990

AGE–SPECIFIC INCIDENCE RATES FOR AGE AT DEATH (PER YEAR)



UNITED KINGDOM 1985 – APRIL 1990

DURATION OF ILLNESS (MONTHS)



An important consideration in assessment of the risk of BSE is the clinical presentation of CJD as there is a theoretical possibility that this might alter if the human population were affected by a zoonotic strain of infectious agent. The clinical features in the 1985-90 survey are summarised in Tables 6 & 7.

TABLE 6

1985 - APRIL 1990 SURVEY
(n = 138)

Clinical Features

	No.	Not Present	%
Myoclonus	108	22	83
Cortical blindness	10	119	8
Pyramidal signs	72	54	57
Extra-pyramidal signs	45	82	35
Cerebellar signs	82	50	62
(Focal signs)	127		92
Akinetic mutism	95		76
Wasting	1	123	1

TABLE 7

1985 - APRIL 1990 SURVEY

Investigations

			% (n = 125)	% (n = 138)
EEG	Typical	= 86	69	62
	No EEG	= 11	-	8
	Normal	= 0	-	0
	Slow	= 39	31	28
	No info	= 2	-	1

(Total number of cases with EEGs = 125)

The frequency of suggestive clinical features including myoclonus, pyramidal signs and akinetic mutism are entirely comparable to previous investigations including that between 1970-79 in England and Wales. The frequency of characteristic EEG is also comparable.

2. Prospective Study of Creutzfeldt-Jakob Disease in the United Kingdom - 1st May 1990 - 30 April 1992

The methodology of the prospective survey parallels that previously established by Professor Matthews. Neurologists, neurophysiologists and neuropathologists are regularly circularised and asked to refer all suspect cases of CJD. The centre is visited by the Research Registrar (Dr T.F.G. Esmonde), who examines the patient, looks through the investigations including EEG and carries out a standard questionnaire with a relative. An age- and sex-matched control case is identified and the standard questionnaire is carried out with a relative of the same degree whenever this is possible. As a safety net, all death certificates mentioning CJD are obtained regularly from OPCS and equivalent bodies in Scotland and Northern Ireland.

The main purpose of the investigation is to determine whether there is any change in a number of epidemiological parameters of CJD including numbers of cases, geographical distribution of cases and occupational incidence.

Between 1st May 1990 and 30th April 1992, 139 cases were referred with suspect CJD. These have been subsequently classified according to the standard diagnostic criteria to give a total of 43 definite cases and 11 probable cases over the 2-year period (Table 8).

TABLE 8

PROSPECTIVE SURVEY 1 MAY 1990 - 30 APRIL 1992

139 Notified

43 Definite cases
11 Probable cases
20 Possible cases
63 Others
2 Not classified (identified from death certificates - not enough information)

The total number of cases for the second year of the study is likely to rise as post mortems have been carried out on a proportion of the 20 possible cases, including 4 in which there is pathological material available in Edinburgh. Two cases ascertained from death certificates have not been classified as we do not yet have sufficient information. It is also important to stress the importance of the 63 suspect cases classified subsequently as being non-CJD as this is consistent with the previous prospective survey and indicates that a broad spectrum of unusual cases of dementia are being referred.

Of the 139 notified cases, 108 have died and of these 76 have had a post-mortem with an overall post-mortem rate of 70%.

Of the 54 definite and probable cases, 29 died in the first year of the study and 25 in the second year of the study. The latter figure is likely to rise as we obtain more post-mortem information on possible cases. However the overall incidence of 0.45 cases/million/year does not suggest any increase in the numbers of cases of CJD with time. This is further documented in Table 9 which shows the annual numbers of deaths from Creutzfeldt-Jakob disease from 1970-1991. The lower figures in the 1970s which gradually increase towards the end of the decade almost certainly indicate an increased recognition of CJD by neurologists with time. This finding has been paralleled in previous surveys including that in France. The numbers of cases per annum show no significant increase from 1978 onwards and this is despite the differing methodologies of the various studies during this period and the different population bases (the numbers of cases in Table 9 relate to annual incidence/calendar year in contrast to the figures quoted above which relate to annual incidence in the prospective survey running from May - April each year).

Geographical distribution of CJD in 1970 - 30 April 1992.

The geographical distribution of cases of CJD is illustrated in figures 1, 2, 3 and 4 covering 4 epochs of the study of CJD. Scotland and Northern Ireland were not studied in 1970-79 and were only studied retrospectively between 1980 and April 1990 in contrast with England and Wales which was studied prospectively for the period 1980-1984.

TABLE 9

DEATHS FROM CREUTZFELDT-JAKOB DISEASE (DEFINITE & PROBABLE CASES) 1970-1991

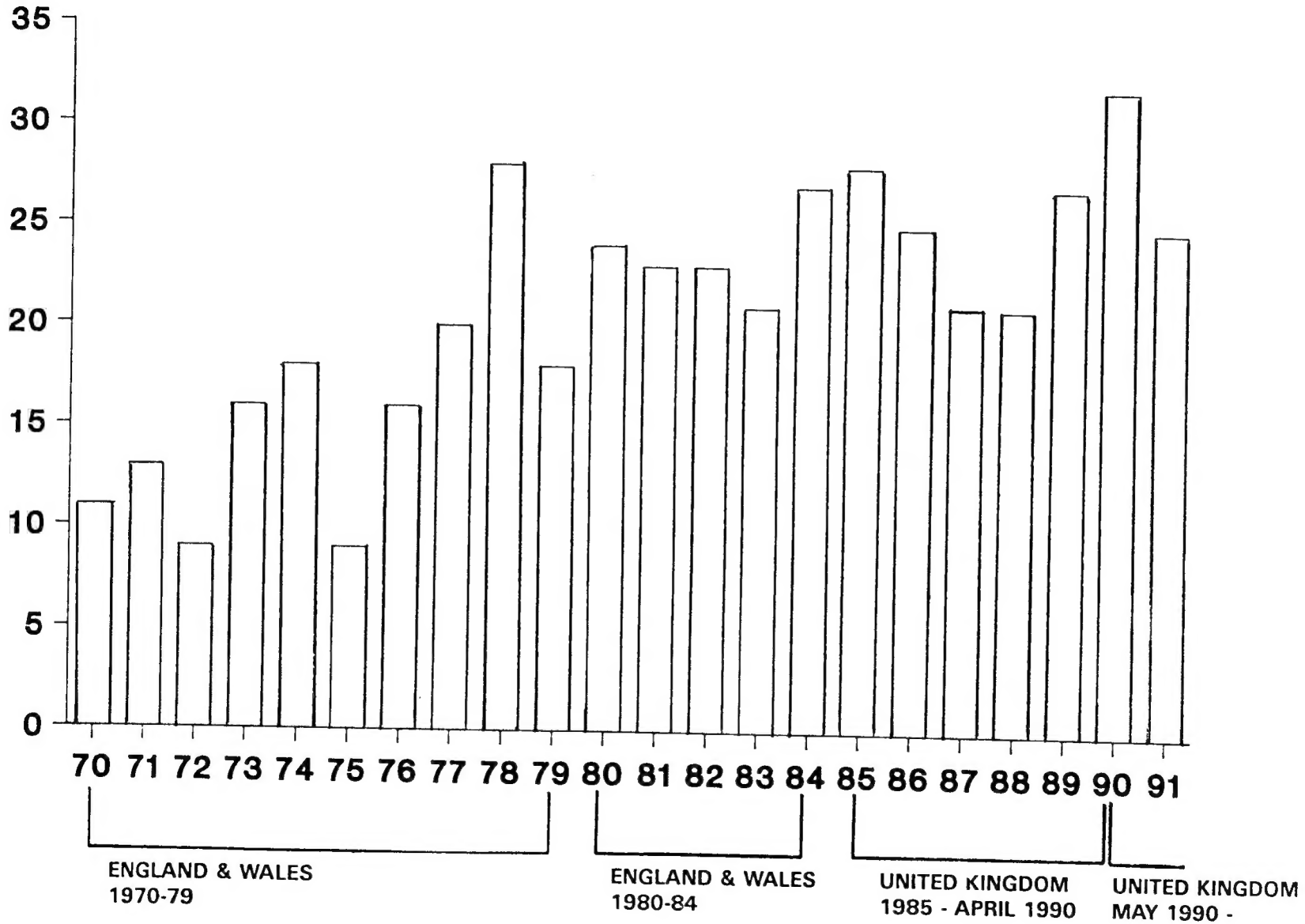


FIGURE 1

SURVEILLANCE OF CREUTZFELDT–JAKOB DISEASE DEFINITE AND PROBABLE CASES DYING IN THE PERIOD 1970–1979 (ENGLAND AND WALES)

FIGURE 2

SURVEILLANCE OF CREUTZFELDT–JAKOB DISEASE DEFINITE AND PROBABLE CASES DYING IN THE PERIOD 1980–1984 (ENGLAND AND WALES)

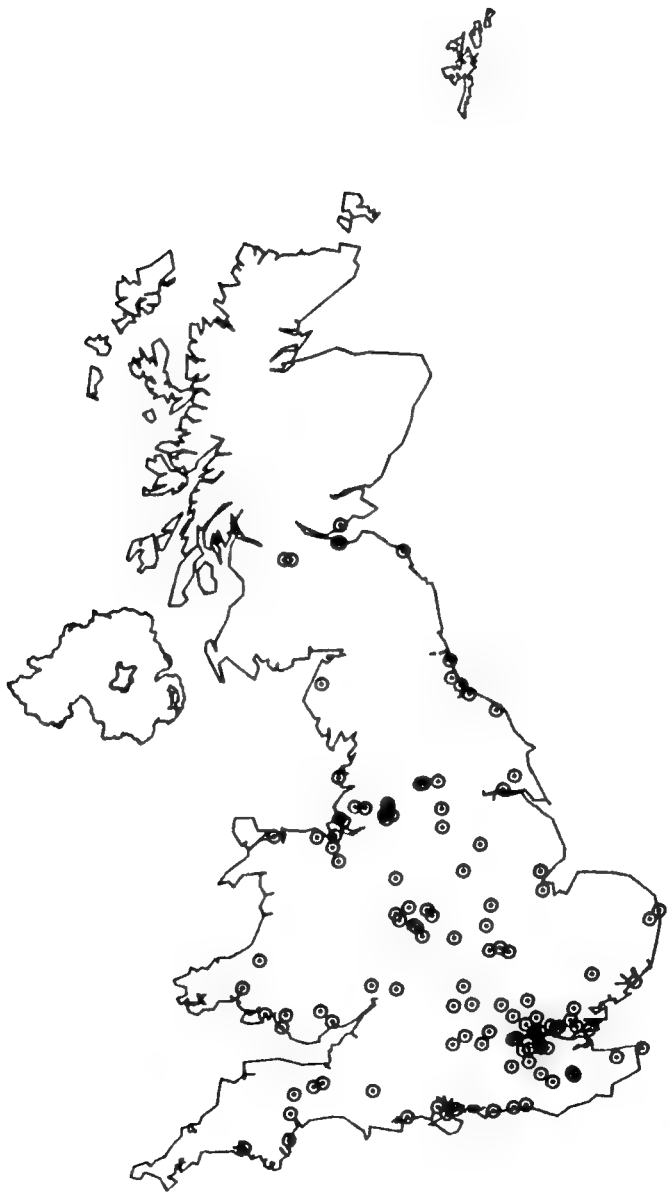


FIGURE 3

SURVEILLANCE OF CREUTZFELDT–JAKOB DISEASE DEFINITE AND PROBABLE CASES DYING IN THE PERIOD 1985 – APRIL 1990 (UNITED KINGDOM)

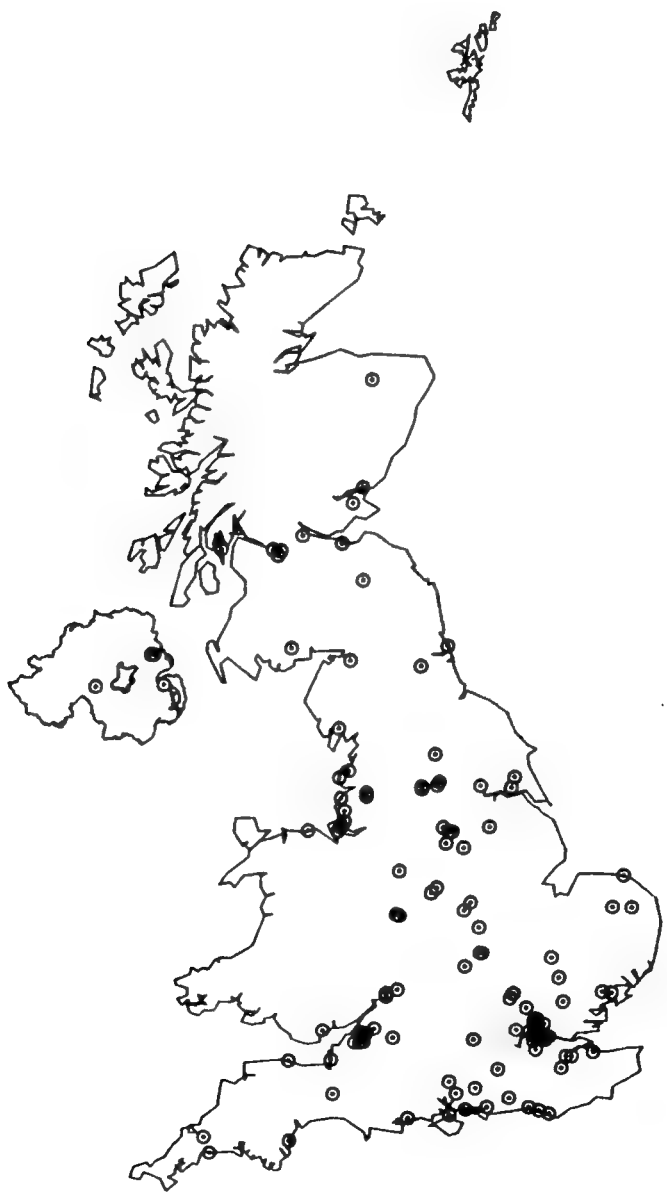


FIGURE 4

CREUTZFELDT–JAKOB DISEASE (1 MAY 1990–30 APRIL 1992)
DEFINITE (n=43) AND PROBABLE (n=11) CASES

LEGEND

- Definite cases
- Probable cases

Formal analysis of the geographical distribution has been carried out for the period 1970-1984 in England and Wales and showed no significant spatio-temporal aggregation of cases. Provisional analysis for the United Kingdom between 1985 and April 1990 has shown no significant aggregation with the exception of a small excess of cases in one area of London and in the Bristol area. The latter may be due to lack of information on place of residence of two cases while the occurrence of an excess of cases in London is not unexpected either as a chance phenomenon or in comparison with studies in France which showed an excess of cases in the Paris region. The geographical distribution between May 1990 and 30 April 1992 has not been formally analysed but shows no obvious aggregation of cases and in particular no excess of cases in the Southern counties of England with a higher incidence of BSE. The map also indicates that cases of CJD are being referred from throughout the United Kingdom.

Occupational Incidence.

Of the 54 definite and probable cases, detailed occupational histories are available on 43. The reason for this is that the relatives of some cases ascertained after death or from death certificates have not yet been interviewed.

Certain specific occupations have been flagged and of the 43 cases with a detailed occupational history, the numbers of cases in specific "at risk" occupational groups are listed below:

Of the 43 -

8	Medical/Paramedical/Nursing/Dentistry
1	Animal Laboratory
0	Pharmaceutical Laboratory
0	Research Laboratory
2	Farmers/Vets
2	Butchers/Abbatoir workers or other occupation with direct contact with animals/carcasses
4	Occupation involving animal products

Medical/Paramedical/Nursing/Dentistry

Case No.	Occupation
1	Health Clinic cleaner
7	Nurse
10	Nursing auxillary
14	Nursing auxillary in theatres
50	Doctor's receptionist/records
73	Hospital domestic
105	Hospital dietician
115	Nurse

TOTAL = 8

Animal Laboratory

Case No.	Occupation	
86	Animal laboratory assistant	1958-1979

TOTAL = 1

Pharmaceutical Laboratory TOTAL = 0

Research Laboratory TOTAL = 0

Farmers/Vets

Case No.	Occupation	
56	Farmhand	pre 1949
136	Farm worker	pre-war

TOTAL = 2

Butchers/abbatoir workers or other occupation involving direct contact with animals/carcasses

Case No.	Occupation	
75	Capstan lathe worker	1938-40
110	Pet shop/Gardening shop	1940

TOTAL = 2

Occupation involving animal products

Case No.	Occupation	
10	Sausage factory worker	pre-1978
89	Warehouse foreman in wool factory	1957-1990
44	Manufacturing pig meat products	1935-47 & 1970-75
74	Wool packer	1976-1985

TOTAL 4

The animal laboratory worker worked in a school laboratory between the years 1958 to 1979. Of the two farm workers, one worked as a farmhand prior to 1949 and the other pre-War, many years prior to the advent of BSE. It is also of course important to stress that obtaining a detailed occupational history will result in the inevitable occurrence of specific potentially at risk occupational groups in the study population. This underlines the importance of the case-control study and relevant findings are tabulated below:

Of 54 definite and probable cases, we have controls for 39.

Of these 39 -

	Case	Control
Medical/Paramedical/Nursing/Dentistry	6	4
Animal Laboratory	1	0
Pharmaceutical Laboratory	0	0
Research Laboratory	0	0
Farmers/Vets	1	5
Butchers/Abbatoir workers or other occupation with direct contact with animals/carcasses	2	1
Occupation involving animal products (eg leatherworker)	4	2

3. Conclusions

Descriptive epidemiological data is now available on Creutzfeldt-Jakob disease in the United Kingdom between 1980 and April 1992. There has been no significant change in the incidence of Creutzfeldt-Jakob disease, the clinical features of Creutzfeldt-Jakob disease, or the geographical distribution of cases. Analysis of the occupational distribution of cases in the first two years of the prospective study, including a case-control study, shows no significant increase in the risk of Creutzfeldt-Jakob disease in relation to specific occupations. There is currently no evidence of any change in the epidemiological characteristics of Creutzfeldt-Jakob disease following the advent of Bovine Spongiform Encephalopathy.

APPENDIX 1

STANDARDISED CRITERIA FOR DIAGNOSIS

CRITERIA FOR THE CLASSIFICATION OF CASES OF CJD

Definitive criteria for the diagnostic classification of CJD were established by Masters et al in 1979[1]:

1. Transmissible virus dementia

   Cases experimentally transmitted to nonhuman primates and/or other animals, producing an experimental spongiform encephalopathy.

2. Definite or probable CJD

   A. Definite CJD

      Neuropathologically confirmed spongiform encephalopathy in a case of progressive dementia with at least one of the following features:

      1. Myoclonus
      2. Pyramidal signs
      3. Characteristic EEG
      4. Cerebellar signs
      5. Extrapyramidal signs

   B. Probable CJD

      Neuropathologically unconfirmed cases with the same clinical features as 2A.

3. Possible CJD

   History, without medical records allowing confirmation, of progressive dementia with:

   A. Myoclonus and a course of less than three years; or
   B. A member of the family having transmissible, definite or probable CJD; or
   C. At least two of the clinical features listed for 2A together with the appearance of prominent and early signs of lower motor neurone involvement (the amyotrophic form of CJD)

These criteria have been adapted in the light of subsequent developments in the field and the criteria for the classification of cases in both the original and current studies are as follows:

1. Transmissible virus dementia

   Cases experimentally transmitted to nonhuman primates and/or other animals, producing an experimental spongiform encephalopathy.

   NOTE:In the UK there are limited facilities for transmission to marmosets. There are no facilities for transmission of CJD to rodents. Important issues, including the transmission characteristics of CJD, strain-typing, and attempted transmission in cases of specific interest, cannot currently be examined.

2. Definite or probable CJD

A. Definite CJD
Neuropathologically confirmed spongiform encephalopathy in a case of progressive dementia with at least one of the following features:

1. Myoclonus
2. Cortical blindness
3. Pyramidal, cerebellar or extrapyramidal signs
4. Akinetic mutism
5. Characteristic EEG

NOTE: Analysis of the clinical features in systematic surveys of CJD suggests that cortical blindness and akinetic mutism are important and relatively specific diagnostic criteria.

B. Probable CJD
Neuropathologically unconfirmed cases with at least two of the clinical features mentioned above and the characteristic EEG.

NOTE: The presence of the characteristic EEG has proven to be an accurate, but not absolute, indicator of the presence of typical pathological changes. Cases which are otherwise typical but do not exhibit the characteristic EEG are classified as "possible" because a significant proportion of these cases are likely to be not-CJD.

3. Possible CJD

Progressive dementia plus three of the above clinical features but either an uncharacteristic EEG or no EEG recording.

NOTE: Possible cases have been excluded from analysis in previous surveys and are excluded from analysis in the current study.

These diagnostic criteria were used in Professor Matthew's study and were discussed at the MRC on 21.10.85: "The diagnostic criteria which were used were satisfactory and easy to apply but there were difficulties in too rigid an application. For example, in otherwise typical cases of comparatively long duration, spongiform degeneration, the major factor used in identifying CJD might not be detected. The diagnostic criteria could be applied to advanced cases or in retrospect but were of little use in the early diagnosis of CJD".

Problems in classification

1. Familial cases
In the previous study in England and Wales all members of pedigrees with CJD were classified according to the above criteria rather than those of Masters et al. This may have led to an underestimate of familial cases (for example the clinical details in old case notes were often sketchy), but it was felt appropriate to apply diagnostic criteria rigidly because of the possibility of attributing the label of CJD to any dementing illness.

Other studies have used the criteria of Masters et al1 which define a case of familial CJD as: an individual with a history of progressive dementia in a family with a known definite or probable case. The prevalence of Alzheimer's disease (DAT) suggests that the concurrence of CJD and DAT may occur by chance and that the use of these criteria for familial CJD may result in an overestimate of familial cases.

2. Amyotrophic CJD
Attempted transmission studies using inocula from this variant of CJD have, almost without exception, been unsuccessful. The consensus is that amyotrophic CJD should not longer be regarded as a transmissible dementia and is therefore excluded from the current study.

3. Iatrogenic cases
The clinical features in human growth hormone recipients who develop CJD are atypical. The clinical diagnostic criteria in this group of patients, and two recent recipients of human gonadotrophin who developed CJD, are not applicable. In these patients the diagnosis of probable CJD rests on the development of a progressive cerebellar syndrome in the context of prior treatment with a pituitary derived hormone. An alternative explanation for the clinical presentation must be excluded eg recurrence of the original condition. Criteria for classification as a "definite" case stand.

Reference

1. Masters CL, Harris JO, Gajdusek DC, Gibbs CJ Jr, Bernoulli C, Asher DM. Cretuzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. Ann Neurol 1979; 5: 177-188.

SECTION 2 NEUROPATHOLOGY VALIDATION

1. Statement of Progress

The CJD Neuropathology Surveillance Laboratory has been functional for one year from May 1991 with the services of one full-time MLSO 2. The lab was set up under the direction of Dr J.E. Bell as specified in the original proposal. The smooth running of the neuropathology component is now dependent on the work of both the Edinburgh consultant neuropathologists - Dr James Ironside contributed to the final planning of the laboratory and is now an indispensible member of the team. The laboratory handles autopsy and occasional biopsy material from both local cases and those collected from collaborating pathologists all over the UK. Protocols have been established for safe handling of tissues, and the performance of full autopsies, with regard to the lastest guidelines from the Advisory Committee on Dangerous Pathogens. Neuropathological verification of CJD cases, both local and referred, is in progress exactly as planned in the original proposal, and diagnostic reports are sent to the referring pathologists.

At the same time, there has been a heavy investment of time in establishing research activities using this resource of CJD tissue. The main thrust of research in the last year has been to establish reliable protocols for prion immunostaining using a variety of prion (PrP) antibodies gifted from Dr J. Hope, Dr S. Prusiner, Professor B. Anderton, Dr H. Diringer and Dr C.J. Gibbs. In addition, work has commenced to elucidate cellular pathology mechanisms in CJD, using antibodies to a variety of neurodegenerative and other proteins. Some of this research work has been handled very capably by a medical student, Mr P. Hayward, who has undertaken an intercalated Honours Degree under the supervision of Drs. Bell and Ironside. The Medical Research Council has asked the Edinburgh neuropathologists to host a workshop to which workers in PrP immunostaining will be invited, to try to establish consensus in staining protocols and agreement about its use in the diagnostic setting.

This expanding research programme has been particularly timely in view of the explosion of knowledge concerning molecular biology in prion diseases, together with the variety of clinicopathological subsets which are beginning to emerge. The Edinburgh neuropathologists expect to make a real contribution to this debate. A major grant has been awarded from the Agricultural and Food Research Council (£231K over 3 years) to Drs. Ironside, Bell and Will and a further grant application has been submitted to the Medical Research Council (Drs. Bell, Ironside and Will), both based on neuropathological research in the human spongiform encephalopathies.

Dr J. Bell has been a member of the ACDP Working Party on Spongiform Encephalopathies which is nearing the completion of its task in drawing up new guidelines for safe handling of spongiform encephalopathy tissues.

Dr J. Bell visited Dr S. Prusiner and Dr S. DeArmond in San Francisco in February 1992 in order to gain first hand experience of immunocytochemistry and other methods in use in their laboratories.

2. Adherence to the Original Plan

It is undoubtedly true that this project has entailed considerably more work for the neuropathologists than was originally envisaged. The number of referrals is larger than expected and the opportunity to perform very detailed autopsies in cases brought into Edinburgh has proved time consuming but has also provided much valuable research material which is stored in a variety of ways so that the potential for future research is maximised. The help of Dr J. McLaughlin, at the Royal Free Hospital in London, has recently been enlisted and he will act as the co-ordinator for autopsies in the South of England. This will increase the opportunity of obtaining research material from CJD autopsies, rather than limiting the autopsy to removal of the brain. Some small extra costs (£2,500 pa) have been requested to facilitate autopsy examinations in Edinburgh and in the Royal Free Hospital.

It has become essential to have extra secretarial help for the neuropathological arm of the survey in view of the documentation required. This includes protocols, reports to collaborating pathologists, response to requests for advice and general coordination of the neuropathological activities. An extra half-time secretary is to be employed.

The additional laboratory personnel who will be required to undertake the increasing burden of research activities are to be funded from the research grants.

In summary, the only departure from the original plan is in terms of expansion due to larger than expected workload.

3. Publications and Presentations

Department of Health National Surveillance of Creutzfeldt-Jakob Disease. Bell JE and Ironside JW. Bulletin of the Royal College of Pathologists, April 1991, pp 9-10.

Bell JE, Ironside JW, McCardle L & Will RG. Creutzfeldt-Jakob disease - UK Neuropathology Project. Neuropathology and Applied Neurobiology 1992; 18: 302.

Ironside JW, Bell JE, McCardle L & Will RG. Neuronal and glial reactions in Creutzfeldt-Jakob Disease. Neuropathology and Applied Neurobiology 1992; 18: 295.

Ironside JW, McCardle L, Hayward P & Bell JE. Ubiquitin immunocytochemistry in human spongiform encephalopathies. (Submitted to Neuropathology and Applied Neurobiology).

Prion Protein: Distribution and Significance in Creutzfeldt-Jakob disease - Thesis submission by Philip Hayward for Degree of Honours BSc (Medical Science) in Department of Pathology.

Invited Talks and Presentations

Institute of Neurological Sciences, Glasgow (Bell JE & Will RG), December 1991.

University of Nottingham (Ironside JW), June 1992.

University of Berlin/European Congress of Neuropathology (Ironside JW), July 1992.

4. Data on Number of Cases in the Surveillance Studies (to 30 April 1992)

Total number of cases examined	72
Suspected CJD cases which have been referred	60
Full autopsies performed in Edinburgh	12
Cases confirmed as CJD	51

Of the remaining cases, 3 are in the process of being reported, 14 have other forms of dementia and 4 cases have atypical neuropathological findings. Detailed clinicopathological correlation is in progress

All these figures include archival material from cases ascertained in the last 5 years and do not just refer to the surveillance period May 1990 onwards.

SECTION 3 GENETIC STUDIES IN CREUTZFELDT-JAKOB DISEASE

With the permission of the referring clinician and the signed permission of a relative, blood has been taken from each suspect case for research purposes. Although serum, urine and CSF are regularly stored, these specimens have been kept for future analysis. Following Ethical Approval on two occasions from the Lothian Health Board Ethics Committee, DNA extracted from the blood specimens was examined over the first 14 months of the project by Dr J. Collinge and Professor Anita Harding in London for mutations of the PrP gene. Three such mutations were discovered in the first 31 cases including a Codon 200 mutation, a Codon 178 mutation and a novel insert. Subsequently DNA has been extracted in Edinburgh and we are shortly to undertake further screening of these samples with the assistance of Professor Lathe at the Centre for Genome Research in Edinburgh.

SECTION 4 LECTURES GIVEN (DR R.G. WILL)

1990

1. CATE Symposium, 6th-7th June 1990, Birmingham on Scrapie, BSE & Creutzfeldt-Jakob disease. Talk entitled "CJD Epidemiology, Clinical Features and Risk Assessment".

2. International Association of Biological Standardization (IABS) in Co-operation with Ares-Serono Symposia, 8th-9th November 1990, London. Talk entitled "An Overview of Creutzfeldt-Jakob Disease Associated with the use of Human Pituitary Growth Hormone".

3. South of England Neuroscience Association, 9th November 1990, Oxford.

4. Seminar on Bovine Spongiform Encephalopathy, 12th-14th November 1990, Brussels. Talk entitled "Is there a Potential Risk of Transmission of BSE to the Human Population?"

5. 13th Sutcliffe Kerr Lecture, 27th November 1990, Liverpool. Talk entitled "Slow Virus Infections in Humans and Animals".

6. Department of Psychiatry, 5th December 1990, Edinburgh.

7. MRC Seminar on Molecular Approaches to Research in SE in Man, 14th-16th December 1990, London. Talk entitled "The Surveillance of Creutzfeldt-Jakob Disease".

1991

8. Pathological Society of Great Britain and Ireland 162nd Meeting, 3rd-5th January 1991, Cambridge. Talk entitled "An Overview of the Transmissible Spongiform Encephalopathies".

9. St. James's University Hospital Leeds, 13th March 1991. Talk entitled "Spongiform Encephalopathies in Man".

10. Controversies in Neuropsychiatry, Institute of Psychiatry, London, 10th April 1991. Talk entitled "The Spongiform Encephalopathies".

11. British Endocrine Society, 16th April 1991, Brighton.

12. Conference on Human and Zoonotic SE, 22nd-24th May 1991, Bratislava Czechoslovakia. Talk entitled "Epidemiological Surveillance of Creutzfeldt-Jakob Disease in the United Kingdom".

13. Advanced Paediatric Neurology Course, 12th June 1991, London.

14. Newcastle General Hospital Research Discussion Group, 2nd July 1991. Talk entitled "Spongiform Encephalopathies of Man and Beast".

15. Conference on Prion Diseases in Humans and Animals 2nd-4th September 1991, London. Talk entitled "Epidemiology of Creutzfeldt-Jakob Disease".

16. Association of British Neurologists, 5th September 1991, London. Talk entitled "Spongiform Encephalopathy: Clinical Aspects".

17. World Health Organisation Consultation on Public Health Issues Related to Animal and Human Spongiform Encephalopathies, 12th-14th November 1991, Geneva. Talks entitled "Epidemiology of Human Spongiform Encephalopathies" and "Evaluating the Potential Risk of Transmission of BSE to Man (foodborne, and occupational transmission)".

Cont'd/....

Lectures (Continued)

18. Clinical Meeting, Southern General Hopsital Glasgow, 4th December 1991. Talk entitled "Creutzfeldt-Jakob Disease Surveillance".

1992

19. Symposium: Neurology for the General Physician, 6th March 1992, Glasgow. Talk entitled "Spongiform Encephalopathies - Recent Advances".

20. Royal College of Physicians of Ireland, 13th-14th May 1992, Dublin.

21. BSc (Hons) Neuroscience Course, 13th May 1992, Edinburgh. Talk entitled "Dementia and the Relationship between Human and Non-Human Spongiform Encephalopathies".

22. Rehabilitation Studies Unit, Astley Ainslie Hopsital, Edinburgh, 28th May 1992. Talk entitled "Bovine Spongiform Encephalopathy".

23. International Meeting on Transmissible Spongiform Encephalopathies - Impact on Animal and Human Health, 23rd-24th June 1992, Heidelberg. Talk entitled "Iatrogenic Transmission of Creutzfeldt-Jakob Disease".

24. The British Council - Immunology and the Nervous System: Clinical Aspects, 5th-10th July 1992, Oxford. Talk entitled "The Epidemiology of Prion Diseases".

25. Conference on Infections from Animals to Man, 8th July 1992, Birmingham. Talk entitled "Prions in Animals: A Threat to Man?"

26. The Spongiform Encephalopathies - Current Status and Implications for Other Neurodegenerative Disorders, 5th-6th October 1992, Edinburgh. Talk entitled "CJD in the UK".

SECTION 5 PUBLICATIONS

1. Will RG (1990) Prion Disease. Lancet 336: pp369.

2. Will RG (1991) Subacute spongiform encephalopathies. In: Current Medicine 3, Ed. D.H. Lawson, Published: Churchill Livingston, Edinburgh. Chapter 9 pp 127-143.

3. Will RG (1991) Comment: Slow virus infection of the central nervous system. Current Medical Literature (Neurology), Volume 7, Number 3, September 1991, pp 67-69.

4. Will RG (1991) An overview of Creutzfeldt-Jakob disease associated with the use of human pituitary growth hormone. Develop. Biol. Standard Vol 75: 85-86.

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6. Will RG (1991) Epidemiological surveillance of Creutzfeldt-Jakob disease in the United Kingdom. Eur. J. Epidemiol; 7(5): 460-465.

7. Will RG (1991) The spongiform encephalopathies. JNNP 54(9): 761-763.

8. Cull RE, Will RG (1991) Diseases of the Nervous System. In: Davidson's Principles & Practice of Medicine Eds: Edwards CRW, Bouchier IAD Published: Churchill Livingstone, Edinburgh. Chapter 16, pp 811-904.

9. Esmonde TFG, Will RG (1992) Magnetic resonance imaging in Creutzfeldt-Jakob disease. Ann. Neurol; 31(2): 230.

IN PRESS

1. Brown P, Preese MA, Will RG. 'Friendly fire' in medicine: hormones, homografts and Creutzfeldt-Jakob disease. Lancet (in press).

2. Esmonde TFG, Will RG. Transmissible Spongiform Encephalopathies and their Relationship to Human Neurodegenerative Disease. British Journal of Hospital Medicine (in press).

3. Will RG, Esmonde TFG, Matthews WB. Creutzfeldt-Jakob Disease Epidemiology. In: Prion Diseases of Humans and Animals (in press).

PAPERS TO BE SUBMITTED (DRAFTS APPENDED)

Esmonde TFG, Will RG. Creutzfeldt-Jakob Disease and Blood Transfusion.

Esmonde TFG, Will RG. Creutzfeldt-Jakob Disease and Lyophilised Dura Mater Grafts: Report of Two Cases and a Review of the Literature.

SECTION 6 COMMITTEES AND MEETINGS ATTENDED

1. Member of the Department of Health and Ministry of Agriculture Fisheries and Food Spongiform Encephalopathy Advisory Committee (The Tyrrell Committee).

2. Member of the Committee on Safety of Medicines Working Party on Spongiform Encephalopathies.

3. Advisor to the European Community Agriculture and Public Health Subcommittee on Spongiform Encephalopathies.

4. Member of the Office International des Epizooties Expert Group on Bovine Spongiform Encephalopathy (BSE) and Related Diseases.

5. Member of the Department of Health Advisory Committee on Human Growth Hormone Recipients.

6. Co-opted Member of the Allen Committee (MRC Subcommittee on Human Spongiform Encephalopathies).

7. World Health Organisation Consultation on Public Health Issues Related to Animal and Human Spongiform Encephalopathies.

SECTION 7 CONTACTS WITH THE MEDIA

DR JANSSEN	CENTRE FOR DISEASE CONTROL

NEWSPAPER

HILARY RUSSELL	MEDIA RESOURCE SERVICE
ALAN MASSAM	EVENING STANDARD
JOHN HARVEY	FARMERS WEEKLY
ALAN MCDAIRMID	GLASGOW HERALD
MR ERLICHMAN	GUARDIAN
JEAN SMITH	SCOTSMAN
TOM WILKIE	THE INDEPENDENT
MICHAEL HORNSBY	THE TIMES (AGRIGULTURAL CORR)
FLO BARKER	NEWCASTLE JOURNAL
NEIL FRASER	SUNDAY POST
MR HORWITZ	MEDICAL TRIBUNE, NEW YORK
IAN BAILEY	SUNDAY CORRESPONDENT
JEREMY WATSON	SCOTLAND ON SUNDAY
PETER OLDEST	NATURE MAGAZINE
PETER ALLDISS	NATURE MAGAZINE
JEREMY WATSON	SCOTLAND ON SUNDAY
KENNY FARQUHARSON	SCOTLAND ON SUNDAY
LORRAINE FRASER	MAIL ON SUNDAY
MR NOWELL	NATIONAL NEWSAGENCY
MR GILLESPIE	SCOTTISH FARMER NEWSPAPER
JENNY HOPE	DAILY MAIL
JANE BROWN	MEDICAL LABORATORY WORLD
PAULINE HOLT	NEWCASTLE JOURNAL
PAULETTE PRATT	SUNDAY TIMES MAGAZIE
JOHN FURBISHER	SUNDAY TIMES
EDWARD CARR	ECONOMIST

RADIO

CLARE GRIBBIN	LVC RADIO
HELEN MARK	BBC RADIO FOYLE
JEREMY VINE	RADIO 4 TODAY PROGRAMME
STEVE JONES	BBC RADIO WALES
BOB DICKSON	BBC
SUE LITTEDALE	BBC RADIO 4
DAN MACLEOD	CENTERSOUND RADIO
DEBORAH COHEN	BBC RADIO LONDON

TELEVISION

RAY TOSTEVIN	TELEVISION SOUTH WEST
MARK PERROW	BBC NEWS
JUSTIN JONES	ITN
ADRIAN VAN KLAVEREN	BBC NEWS
JAMES WILKINSON	BBC NEWS
JULIE STUDER	TV AM
KAY ADAMS	SCOTTISH TELEVISION
PALLAD GHOSH	BBC
KISANE PRICE	BBC
JAMES FOLUM	ITN
JUDY INGHAM	BBC CARLISLE (N.WEST TONIGHT)
JONATHAN RENOUF	BBC2 NEWSNIGHT

TELEVISION (CONTINUED)

KARRON GARDEN	BBC ESSEX
JOHN BUFFMAN	REPORTING SCOTLAND
CAROL FERGUSON	SCOTTISH FRONTIERS ON MEDICINE
MR JALDEEP	BBC SCOTLAND
BRIAN HARRISON	BORDERS TELEVISION
IAIN ANDERSON	BBC NEWS
SALLY EDEN	TV AM
LUCY HILLMAN	CHANNEL 4 CHECKOUT 92
OLIVER WILSON	CHANNEL 4

This list represents only a proportion of all those journalists and others who have contacted the CJD Surveillance Programme for information and does not represent the journalists and others who called on repeated occasions. There have also been many contacts with members of the general public who have written or telephoned for information and a booklet on Creutzfeldt-Jakob disease has been produced which although primarily aimed at the relatives of affected patients, has been disseminated to other members of the public who have written for information.

SECTION 8 FUTURE PROGRESS

This study has only been possible with an extraordinarily level of co-operation from neurologists, neurophysiologists, neuropathologists and others throughout the United Kingdom. The main disadvantage of the study is that it will have to continue for many years because of the potentially prolonged incubation period in the spongiform encephalopathies.

The major practical problem with continuing the study is attracting suitably qualified individuals to act as the research registrar. Dr Esmonde, who is shortly to leave the project for a Senior Registrar post in Neurology, has worked exceedingly well and exceedingly hard on this project and has sufficient material for an MD thesis on the epidemiology of Creutzfeldt-Jakob disease. In order to attract a research registrar of similar calibre, it is essential to provide a research project which will lead to an MD thesis. Dr Esmonde was able to cover the years 1985-1992 in his research project and it will be impractical for future research registrars to work for a further degree simply on the basis of the epidemiology. It is therefore crucial to offer subsequent registrars alternative aras of research in relation to CJD. In my view it is therefore of vital importance, in the expectation that the ethical issues will be resolved shortly, that PrP gene analysis is carried out in Edinburgh in order that the Research Registrar can study for a further degree in relation to the molecular biology and possibly also clinicopathological correlations of CJD. This will not have any financial implications for the Department of Health as the laboratory equipment and consumables are already funded from other sources. It is also likely that a specific grant application will be made to one of the research funding bodies in the near future with specific reference to molecular biology.

Other research issues to be addressed are an analysis of clinicopathological correlates of Creutzfeldt-Jakob disease pre- and post-BSE and a grant is shortly to be submitted in relation to the transmission characteristics of CJD pre- and post-BSE. An application has also been made to the BIOMED 1 Programme for co-ordination of epidemiological surveillance of CJD in the European Community.